CHAPTER V

CYCLEN-WATER-METHANOL SIMULATIONS

5.1 Calculation Details

The present MC simulations were carried out using the Metropolis procedure [19]. The system consists 1 cyclen molecule in 18.45 mole % solution of methanol (165 water and 37 methanol molecules). The simulations were performed using on experimental density at 298 K 1 atm of 0.96 g/cm^3 [31], leading to the sidelength of the basic box of 19.60 Å. Half of the sidelength was chosen to be the radius of the spherical cut-off. The cyclen molecule was fixed at the center of the basic box and initial configuration of 202 molecules of the solvent were randomly generated.

Due to the slow convergence of the total energy of the system (cyclen-water-methanol interactions) a large number of configurations was required to bring the system to equilibrium (Fig. 5.1). The simulation was carried out for 4.0 x 10^6 configurations and all quantities were evaluated from 2.0 x 10^6 configurations after equilibration.

Since the simulation system consists of 3 species, therefore, five pairs of intermolecular potential functions are required. The water-water [32], water-methanol [33], methanol-methanol [34], and cyclen-water [35] potential functions were taken from literature, and detail informations were summarized in Appendix.

The cyclen-methanol potential function has been newly developed using quantum chemical calculations, and described in the previous chapter.

To evaluate in detail the influence of cyclen molecule on the structure of water-methanol mixture, space around the cyclen molecule was divided into three regions, namely, top, side and plane. Top corresponds to the conical volumes enclosed by rotating a 45° vectors, starting from the molecular center, around the + and - z axes and side corresponds to the volumes between the two vectors. Inside this side region a cylinder of height ±1 Å in the z axis was defined as the plane region (see in Fig. 5.2a).

Consequencely, for all radial distribution functions (RDFs) between atoms or groups of atoms of cyclen and atoms of water (or methanol) the notation $g_{xy}(r)$ will be used, where x can be either the ligand atoms N, C, H_N, H_C, H'_C or M, T, S, P (M =

full cyclen molecule, T = top, S = side and P = plane) and y can be either the O or H atoms of water or the O, C, H_O or H atoms of methanol.
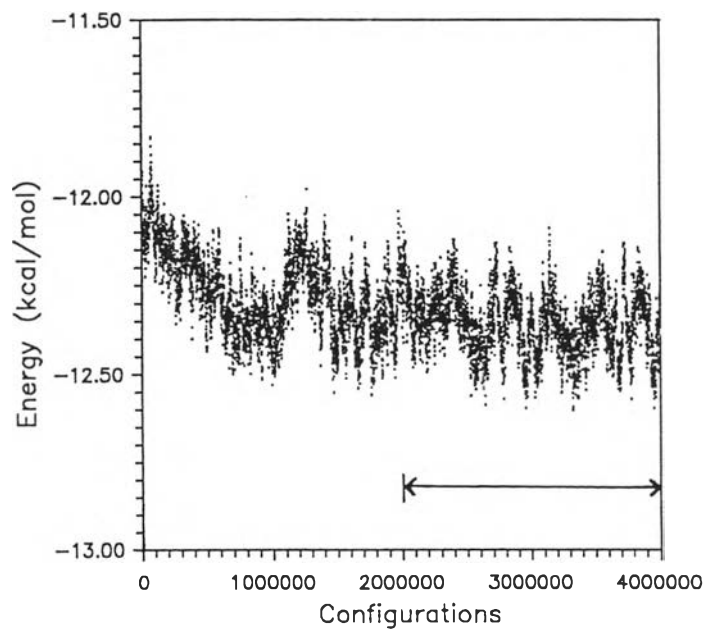

Figure 5.1   Convergence and fluctuation characteristics of the simulations. The arrow mark |↔| shows the range used for the calculation of averaged quantities.

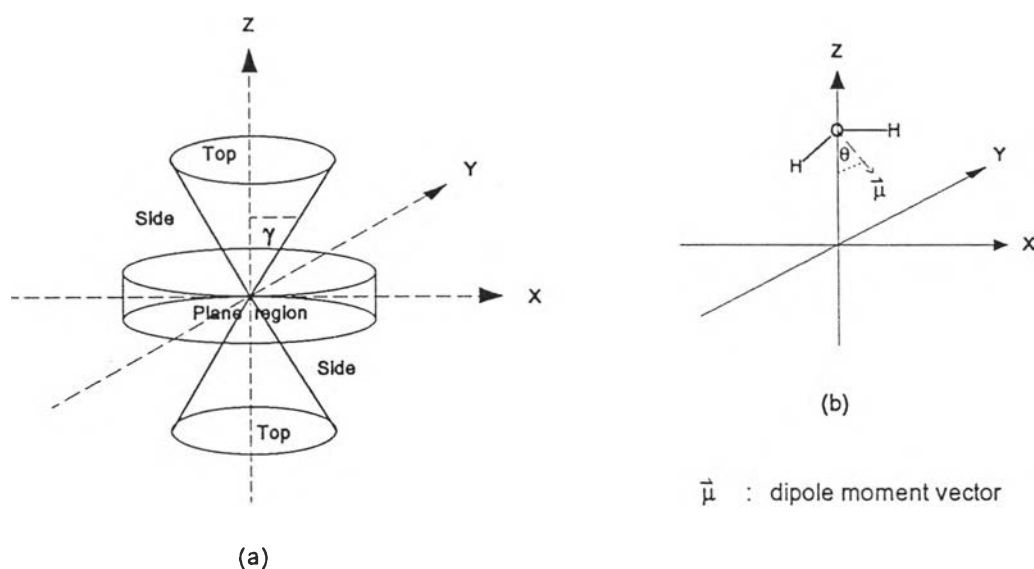Figure 5.2   Definition of (a) the top, side and plane regions ($\gamma = 45°$), (b) the angle θ (for water orientation).

5.2 Results and Discussion

To evaluate the influence of cyclen molecule on the structure of solvent, parallel simulation without cyclen molecule also has been performed.

5.2.1 Solvent Structure

Atom-atom pair correlation functions of solvent molecules, with and without the cyclen molecule, were compared in Fig. 5.3. The differences in the position of these peaks (with and without cyclen) are almost negligible, especially for water-water functions, while the height of each peak for solvents (without cyclen) is slightly higher. The small deviations should be due to the fact that in the presence of the large cyclen molecule the structure of water and methanol molecules in the vicinity of the ligand will be significantly altered, leading to a decrease of the number of water and methanol molecules in an ideal solvent orientation.

The detailed effects of the solute on the structure of water and methanol molecules will be discussed on the basis of the solute-solvent radial distribution functions and the corresponding average coordination numbers, as well as their distribution K , and the distribution of the angle θ (Fig. 5.2b) to evaluate the solvent orientation.

5.2.2 Solvation Structure of Cyclen-Water in Cyclen-Water-Methanol System

The cyclen-water radial distribution functions (RDFs) referring to the center of mass of cyclen (namely top, side, and plane regions compared to the entire molecules) have been separately calculated and plotted in Fig. 5.4. Distribution of coordination numbers up to certain minima are given in Fig. 5.5, of angle θ as defined in Fig. 5.2b, displayed in Fig. 5.6.

The entire RDFs to the center of mass of cyclen $g_{MO}(r)$ (Fig. 5.4d) shows three broad peaks. The first one appears at 2.7-3.0 Å with the corresponding integration number up to 3.4 Å of *ca.* 1, and to 4.0 Å of *ca.* 2. An identical peak, both in terms of peak position and running integration numbers, is found only in the top region (Fig. 5.4a). Therefore, it is clear that these two water molecules are located below and above the ligand's cavity. To understand an unsymmetric distribution of the two water molecules around symmetric ligand, distribution of the water molecules around them, up to the first minimum of the $g_{OO}(r)$ (3.6 Å), has been calculated and depicted in Fig.

5.7. The distribution plotts show clearly that the water molecule (W1) located under the first $g_{MO}(r)$ peak is less solvated by the high coordination numbers, and hence less stable, than the other (W2, centered between 3.4 Å and 4.0 Å) while the average $\overline{K}$ of *ca.* 5.0 for both water molecules is the same. However, it is necessary to fill up the free-space near to the cavity. The unsymmetry of these two water molecules above and below the cavity could be a compromise for this contribution.
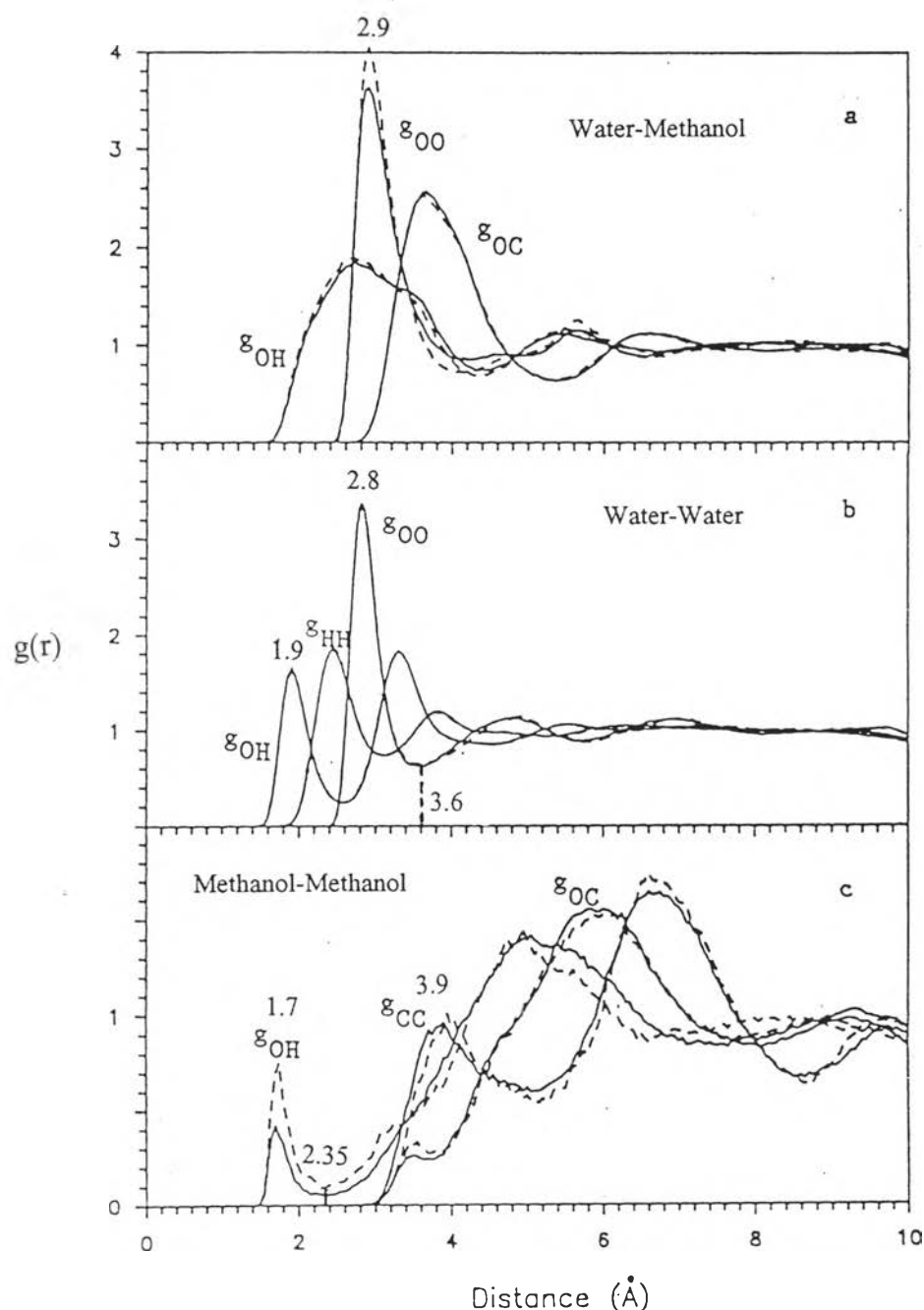

Figure 5.3 Atom-atom pair correlation functions ; (a) water-methanol, (b) water-water and (c) methanol-methanol obtained from the simulations with and without cyclen molecule (solid lines and dash lines, respectively).
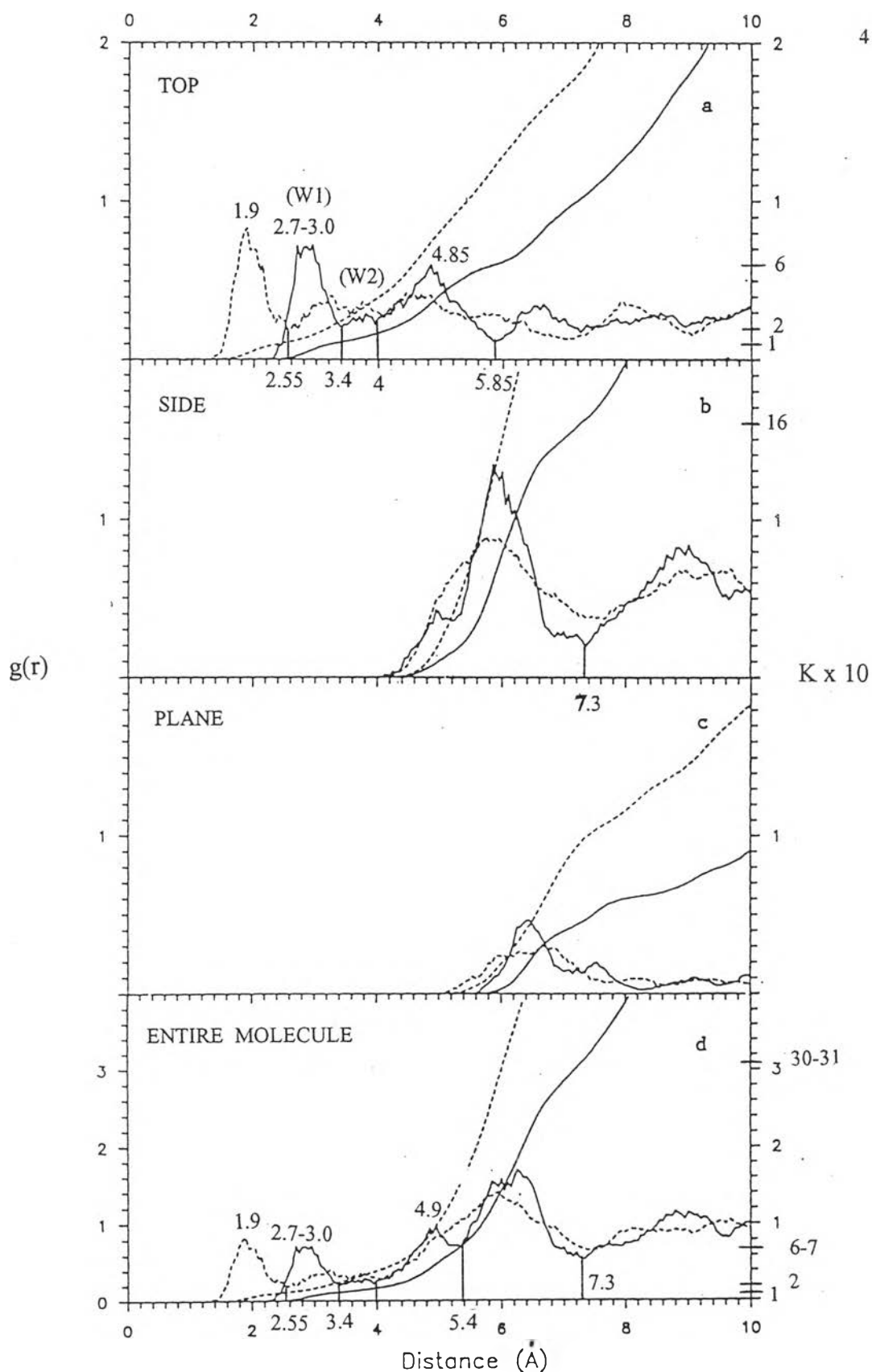
Figure 5.4   Calculated atom-oxygen (—) and atom-hydrogen (---) radial distribution functions and coordination numbers of water molecules for the top (a), side (b), plane (c) regions of cyclen as defined in Fig. 5.2a and for the entire system (d).

In order to evaluate orientation of these two water molecules, detail evaluations were concentrated on the $g_{TH}(r)$ (Fig. 5.4a). The running coordination number integrated up to the first minimum (r_m = 2.55 Å) is *ca.* 1. The corresponding distribution of coordination number (Fig. 5.5f) shows 88 % of K_H= 1 with the average $\overline{K}_H$ of 1.02. The maximum of the distribution of the angle θ (defined in Fig. 5.2b) is *ca.* 50° (solid line in Fig. 5.6). These data and the equivalence between the O-H bond length of water and the difference of the first minima of the $g_{TO}(r)$ and $g_{TH}(r)$ make the conclusion quite convincing that the O-H bond of W1 points toward the center of mass of cyclen with O-H nearly located in the z axis. For W2 located farther way, the broadness of the distribution plot (dash line in Fig. 5.6) with the maximum at *ca.* 48° - 50°, indicates that W2 has more flexible than W1 but still pointing the O-H bond to the center of the cavity of cyclen.
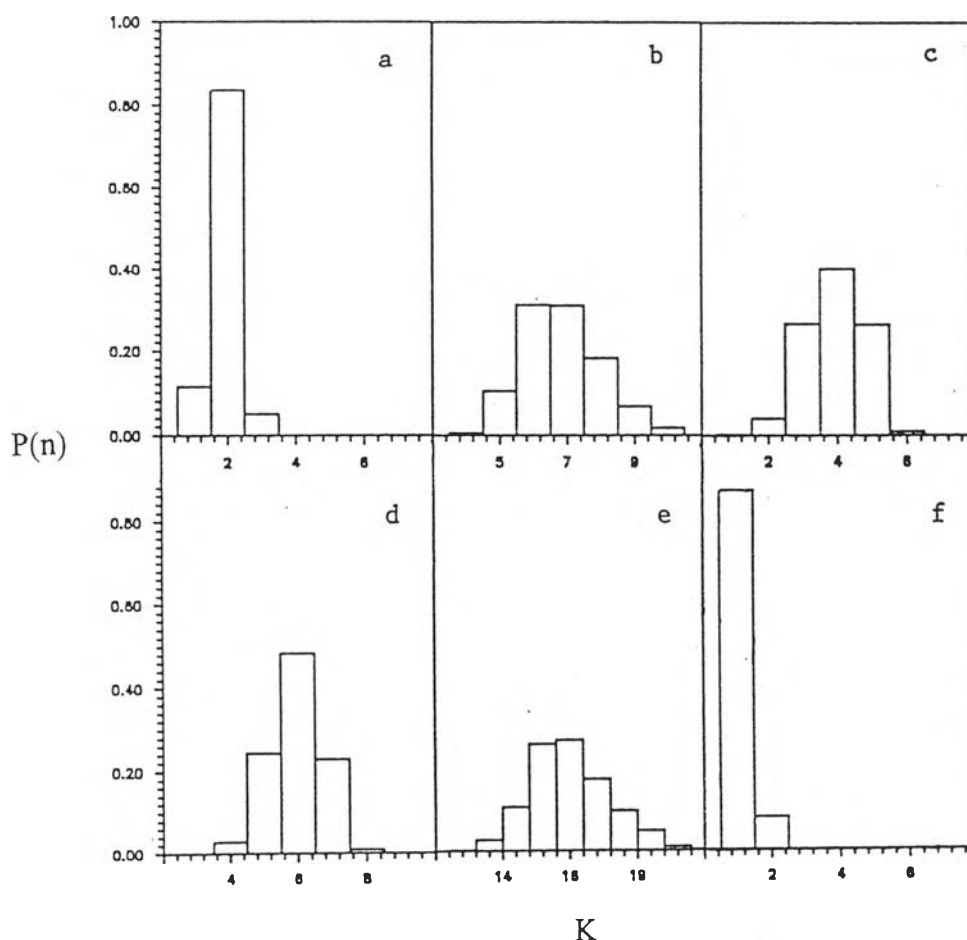

Figure 5.5 Distribution of the oxygen atoms of water (K) around the center of mass of cyclen for the following regions; (a) entire (r_m = 4.0 Å) $\overline{K}$ = 1.94, (b) entire (r_m = 5.4 Å) $\overline{K}$ = 6.84, (c) plane (r_m = 7.3 Å) $\overline{K}$ = 3.93, (d) top (r_m = 5.85 Å) $\overline{K}$ = 6.0, (e) side (r_m = 7.3 Å) $\overline{K}$ = 16.0, and (f) distribution of H atom of water for the top region (r_m = 2.55 Å) $\overline{K}$ = 1.02.
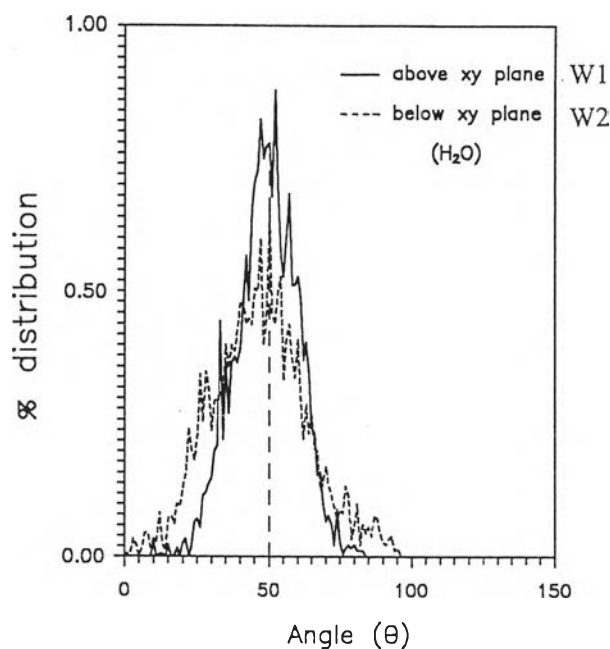
<u>Figure 5.6</u> Distribution of the angle θ as defined in Fig. 5.2b for the top region only for the two water molecules located at the distance less than 3.4 Å (—) and between 3.4 Å to 4.0 Å (---) from the molecular center of cyclen.

The second peak of $g_{MO}(r)$ (Fig. 5.4d) shows the maximum at 4.9 Å and the corresponding integration number of 6-7 (r_m = 5.4 Å). While the equivalent one, $g_{TO}(r)$ (Fig. 5.4a) shows the maximum at 4.85 Å, the running integration number of 6.0 (r_m = 5.85 Å) and the average $\overline{K}_O$ of 6.0 (Fig. 5.5d). It was shown from Fig. 5.4 also that these water molecules do not appear in the plane regions (Fig. 5.4c). All water molecules in the plane region are located farther than 5.6 Å from the center, i.e. the first peak of $g_{PO}(r)$ occurs in the third peak of $g_{MO}(r)$.

The third peak of $g_{MO}(r)$ at 5.8 Å and the last broad peak (Fig. 5.4d) observed in the top, side and plane regions do not give much informations due to their complication. However, it shows that the influence of the cyclen molecule has been observed on the water structure up to 8-9 Å from the molecular center.

As a consequence of the weak cyclen-water interactions (the optimal stabilization energy obtained from the pair potential, E_{op} is -5.5 kcal/mol) which is equivalent to the water-water (E_{op} is -5.9 kcal/mol), and the water-methanol (E_{op} is -5.7 kcal/mol) ones, all peaks of $g_{MO}(r)$, $g_{TO}(r)$ and $g_{SO}(r)$ are broad which indicate that the water molecules are located at quite varying distances from the center of cyclen.

Now the NH functional group will be considered. $g_{NO}(r)$, $g_{NH}(r)$, $g_{H_bNO}(r)$ and $g_{H_bNH}(r)$, together with the corresponding coordination numbers, are given in Fig. 5.8. The distribution of coordination numbers is given in Fig. 5.9.

The $g_{NO}(r)$ (Fig. 5.8a) does not show a real first peak. It is a broad shoulder from 3.0 to 3.5 Å. The running integration number up to r_m = 3.55 Å is *ca.* 1, and the corresponding one for $g_{NH}(r)$ (Fig. 5.8a) up to 3.3 Å is *ca.* 1.7. The N-O distance of 3.15-3.25 Å under small first shoulder of $g_{NO}(r)$ is found to be identical to that of the N-O1 distance (where W1 is in the configuration given in Fig. 5.10). This result has suggested that an appearance of the first $g_{NO}(r)$ peak is the contribution from W1. A further fact, which can be seen from these RDFs is the occurrence of the $g_{NH}(r)$ before the $g_{NO}(r)$ as a contribution with the H1 atom of W1 has pointed toward to the center of cyclen. It is also reasonable to interpret this finding as a contribution with a special orientation, where the H2 atom of W1 has rotated around the z-axis to the region near to the NH groups. Since the second water under the $g_{NO}(r)$ peak, investigated from its integration number, is found between 3.5 Å and 4.0 Å, therefore, it is unusual to report that this water is coordinated to the NH group *via* hydrogen bonding. Because at these distance, hydrogen bonding is no longer valid. The notation W3-W6 is given for this set of water molecules, one for each NH group. Comprehensive investigation on the orientation and coordination of these water molecules have been done in ref.35 and found that they are coordinated to W1 or W2 but not to NH groups. Orientation of W1 or W2 about the z-axis causes also movement and reorientation of these water molecules.
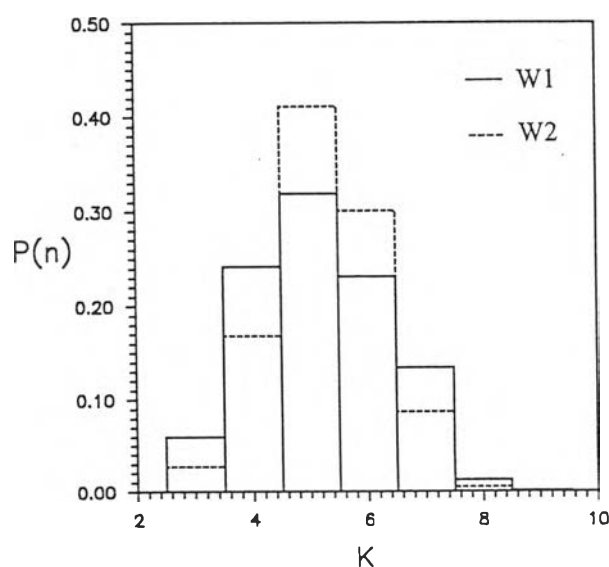

Figure 5.7 Distribution of oxygen atoms of water up to 3.6 Å (the first minimum of $g_{OO}(r)$) around the two oxygens located at the distance less than 3.4 Å (—) and between 3.4 Å to 4.0 Å (---) from the molecular center of cyclen.
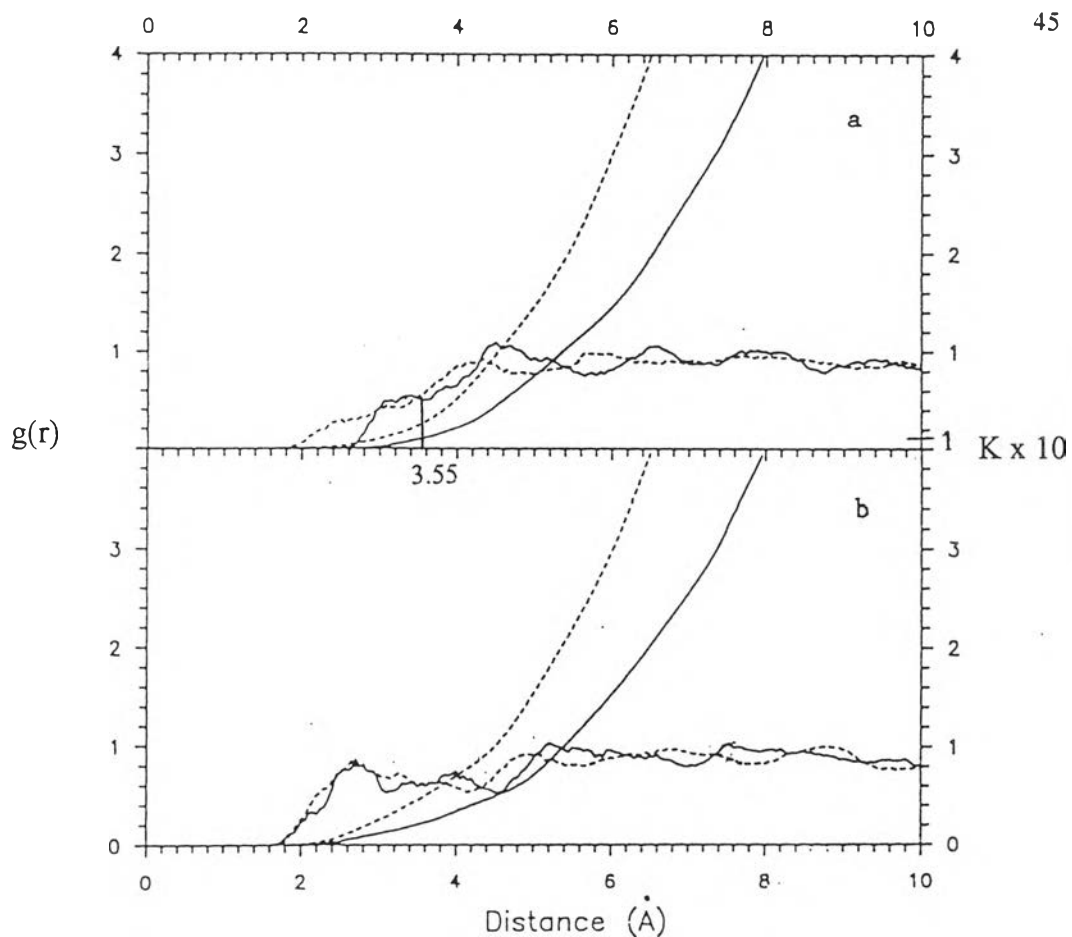
Figure 5.8   Calculated atom-oxygen (—) and atom-hydrogen (---) radial distribution functions and running integration numbers of water molecules for (a) N and (b) H_N atoms of cyclen.
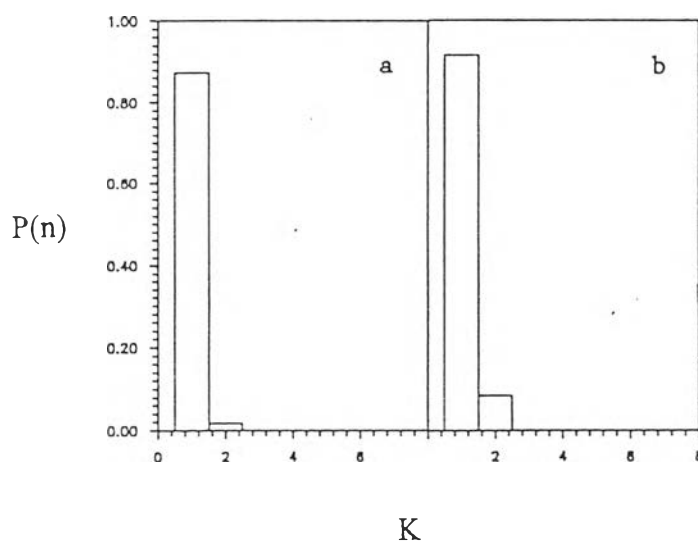

Figure 5.9   Distribution of the coordination numbers of O atoms of water around;
(a) N (r_m = 3.55 Å, $\overline{K}$ = 1.04), and (b) H_N (r_m = 3.1 Å, $\overline{K}$ = 1.3) atoms of cyclen.

Taking into account the whole data we can now suggest the position and orientation of the six water molecules in what could be considered as a first hydration shell of the cyclen, by placing the atoms as indicated in Fig. 5.10. Because of the symmetry of the cyclen we will consider only the three water molecules in one half of the first hydration shell. The first shell coordination number of W1 is *ca.* 5 and two of them are W3 and W4 (see Fig. 5.10). Hydrogen bonding between three of them os also monitored in Fig. 5.10. Alternation of the coordination sites, caused by the rotation of W1, is also possible.
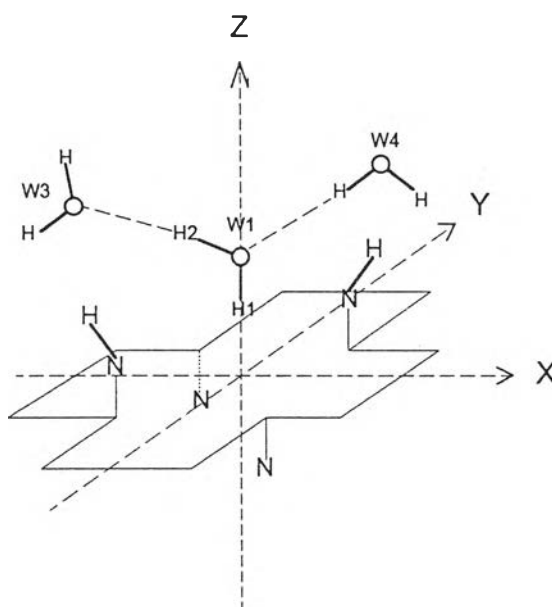

Figure 5.10 Solvation model for water molecules in the first hydration shell of cyclen.

We now consider the CH_2 functional groups of cyclen, for which the RDF data are given in Fig. 5.11 and the distribution of coordination numbers in Fig. 5.12. The six RDF peaks are quite well pronounce but extended to 4.0 Å for H_C and H'_C and to 5.4 Å for C atoms. At these distances, the RDFs will be mixed with that of other atoms. Therefore, these functions give little orientational information. However, the existence of a peak structure proves that the cyclen molecule still influences the water structure slightly at larger distances from the hydrophobic groups.
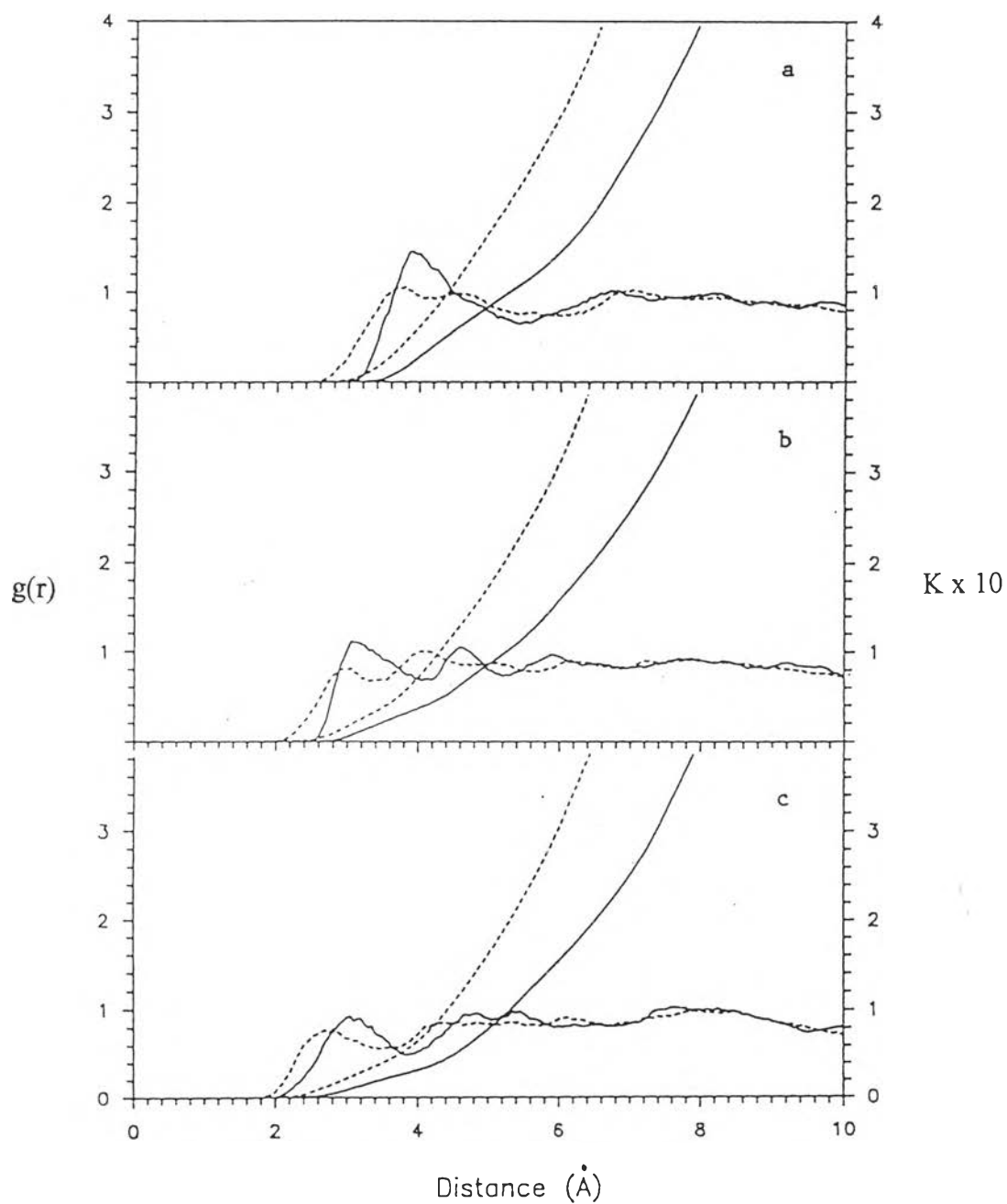
Figure 5.11 Calculated atom-oxygen (—) and atom-hydrogen (---) radial distribution functions and running integration numbers of water molecules for (a) C , (b) H_C and (c) H'_C atoms of cyclen.
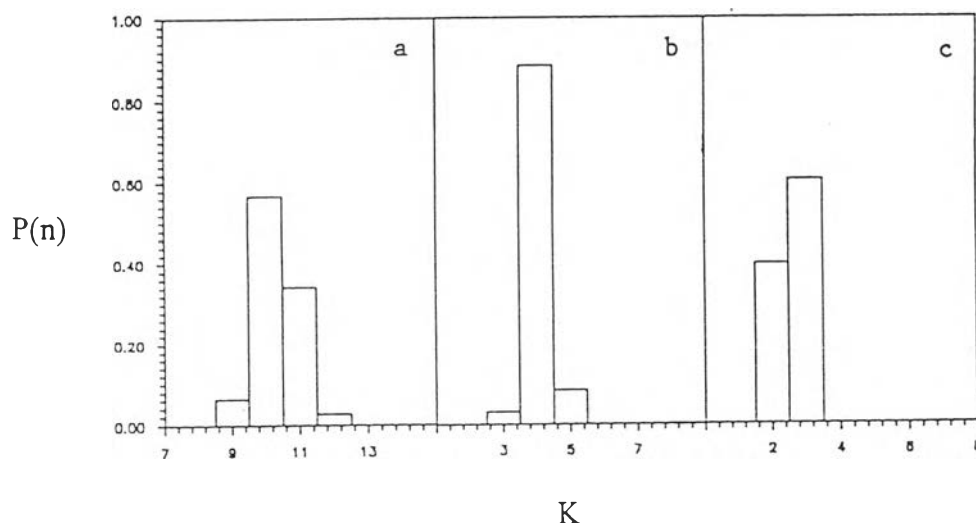
Figure 5.12 Distribution of the coordination numbers of O atoms of water around ;
(a) C (r_m = 5.4 Å, $\overline{K}$ = 10.7), (b) H_C (r_m = 4.2 Å, $\overline{K}$ = 4.3), and (c) H'_C (r_m = 3.8 Å, $\overline{K}$ = 2.7) atom of cyclen.

5.2.2 Solvation Structure of Cyclen-Methanol in Cyclen-Water-Methanol System

The consideration will be the same feature as in the case of the water molecules. The distribution referring to the center of mass of cyclen is given in Fig. 5.13. The distribution of coordination numbers is given in Fig. 5.14.

The $g_{MO}(r)$ (Fig. 5.13d) shows the three broad peaks far from the center of cyclen. The first one varying from 5.0 Å to 6.9 Å displays the running integration number of *ca.* 1. The methamol molecules lying in this area contribute almost to the first peak of $g_{TO}(r)$ (Fig. 5.13a) but not for the other regions.

To ascertain more detail of certain coordination of this methanol molecule, investigation has been done by searching through the " *history file* " (output file which collects coordinate of all atoms for two million configurations). It is found that this methanol molecule is the first solvation shell of W2, binding together as the hydrogen

bonding in the configuration shown in Fig. 5.15. The well pronounce of the first peak of $g_{TO}(r)$ and $g_{MO}(r)$ (Fig. 5.13a and 5.13d, respectively) can be understood from this fact. This finding is clearly consistence with the pronounce peaks of the $g_{NO}(r)$ and $g_{H_NO}(r)$ (Fig. 5.16a and 5.16b) with the integration numbers, for both cases, of *ca.* 0.3. This small number is the consequence of the rotation of the water-methanol dimer about the z-axis. In addition, such behavior is not observed for W1 (see Fig. 5.10) due to the lack of free space around it, since it is very close (2.7 Å) to the cyclen's cavity.

Up to 8 Å from the center of cyclen, it is the area of the second peak of the $g_{MO}(r)$ (Fig. 5.13d). Methanol molecules located in this area contribute to all RDFs. The integration numbers of 4.6 up to 8.05 Å of the $g_{MO}(r)$ correspond to the contribution from 2.9, 1.5 and 0.2 for the top, side and plane regions, respectively. At this distance, as well as those for the third peaks, the solvation shell consists of both water and methanol molecules. It is quite complicate to analyse detail structure in this region.

Consider the RDFs centering to the NH functional groups, the first small and pronounce peaks of $g_{NO}(r)$ and $g_{H_NO}(r)$ (Fig. 5.16a and 5.16b, respectively) are clearly contributed from the equivalent set of methanol molecule which have been discussed and monitored in Fig. 5.15. No more information can be extracted from these functions and those for C and H atoms of methanol given in Fig. 5.17, and those centered to CH_2 functional groups of cyclen given in Fig. 5.18 and 5.19 because of their complexity. However, the existence of a peak structure proves that cyclen molecule still influences the methanol structure slightly at larger distances from the hydrophobic groups.

Some comments could be made concerning the observed structure, which is considered as the solvation shells of cyclen. Consequencely, the RDFs for solvents show an ideal bulk characters, except those of methanol-methanol. Only about 6 water molecules is really influenced by cyclen molecules, the remaining solvents are arranged in the way to form hydrogen bond network with the central water molecules.
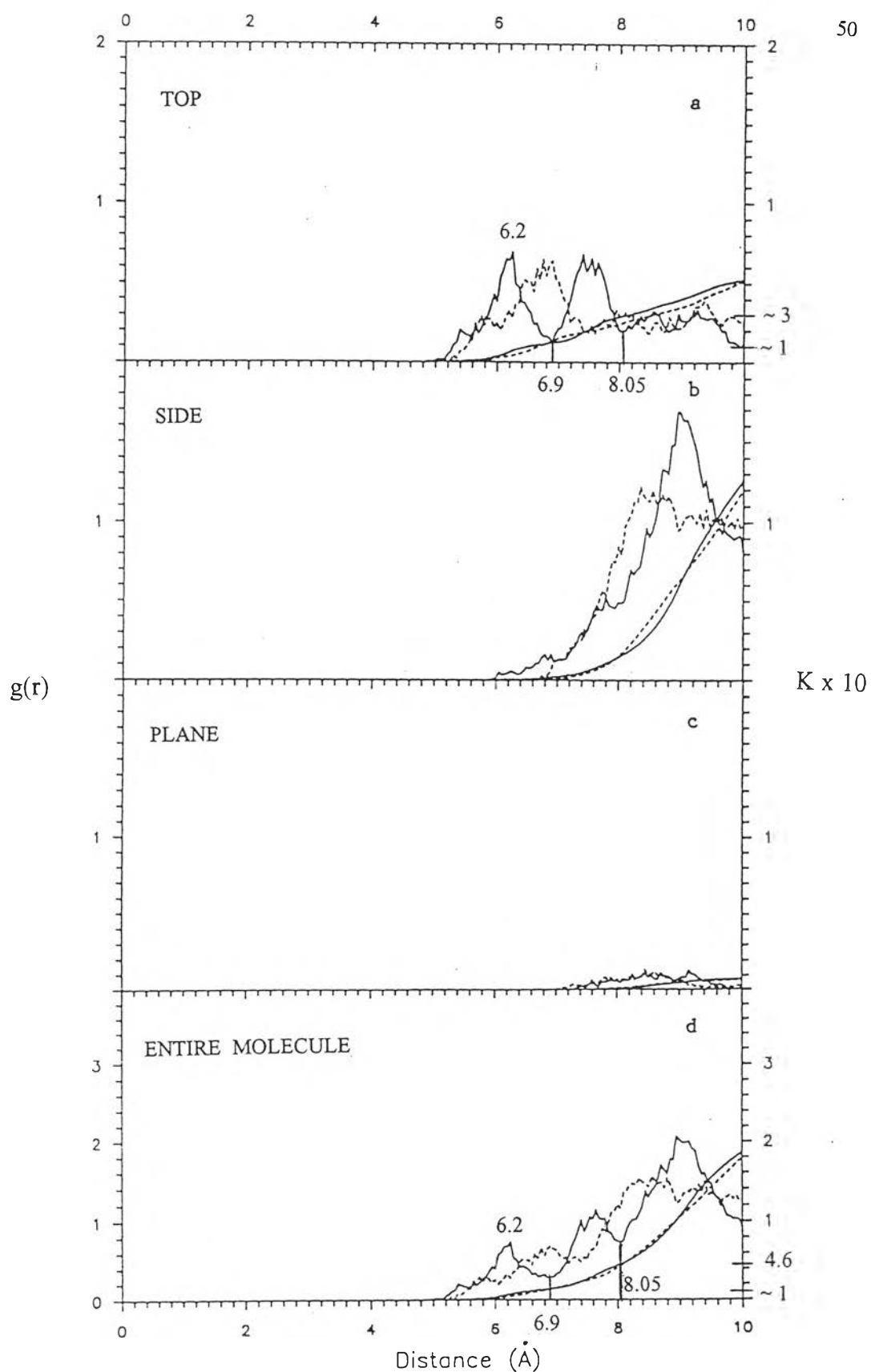
Figure 5.13 Calculated atom-O (—) and atom-H_O (---) radial distribution functions and coordination numbers of methanol molecules for the top (a), side (b), plane (c) regions of cyclen (see Fig. 5.2a) and for the entire system (d).
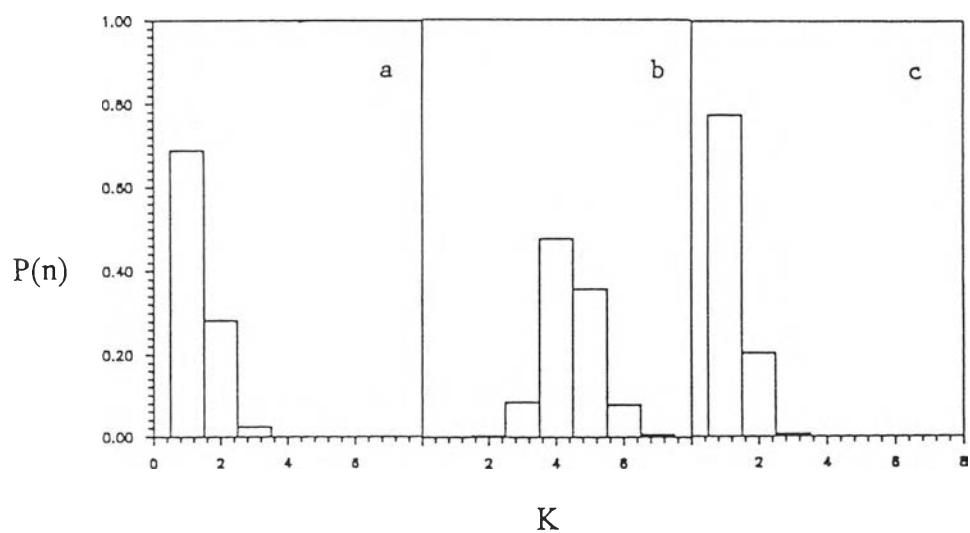
Figure 5.14 Distribution of the coordination numbers around the center of mass of cyclen for the following regions; (a) entire (r_m=6.85 Å) $\overline{K}$ = 1.3, (b) entire (r_m=8.05 Å) $\overline{K}$ = 4.6, and (c) top (r_m=6.9 Å) $\overline{K}$ = 1.2.
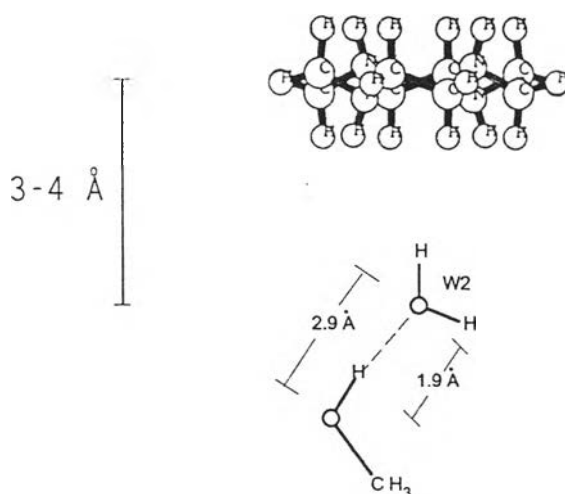
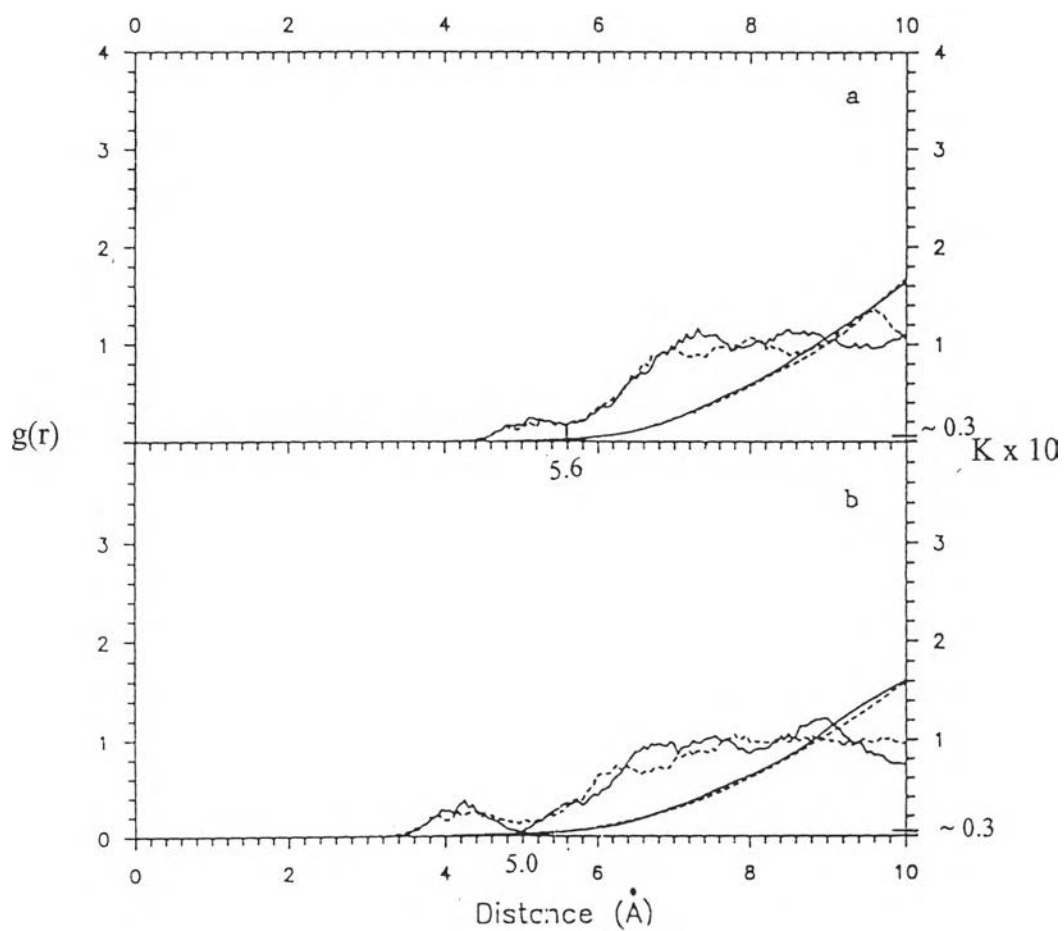Figure 5.15 The proposed binding of methanol molecule, centered in the second shell of cyclen, to W2 (see Fig. 5.10).

Figure 5.16 Calculated atom-O (—) and atom-H_O (---) radial distribution functions and running integration numbers of methanol molecules for (a) N, and (b) H_N atoms of cyclen.
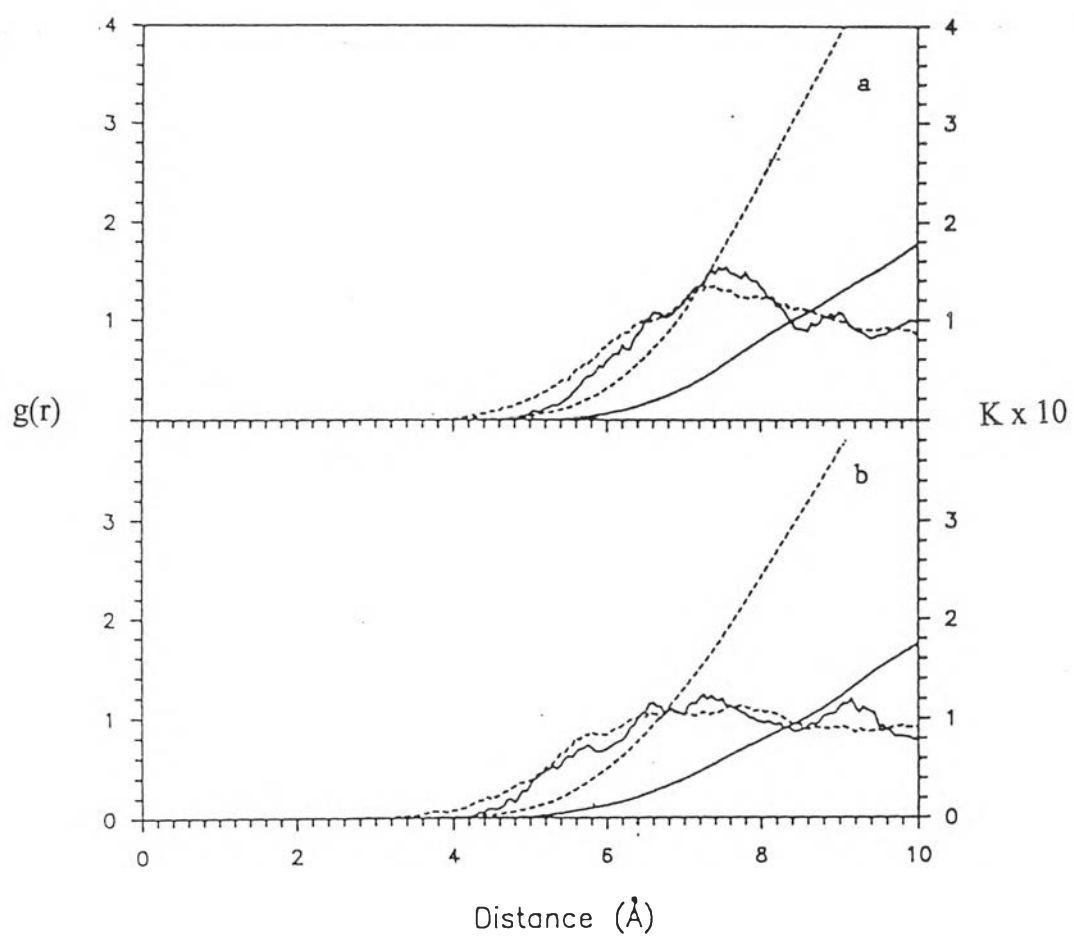
Figure 5.17 Calculated atom-C (—) and atom-H (---) radial distribution functions and running integration numbers of methanol molecules for (a) N, and (b) H_N atoms of cyclen.
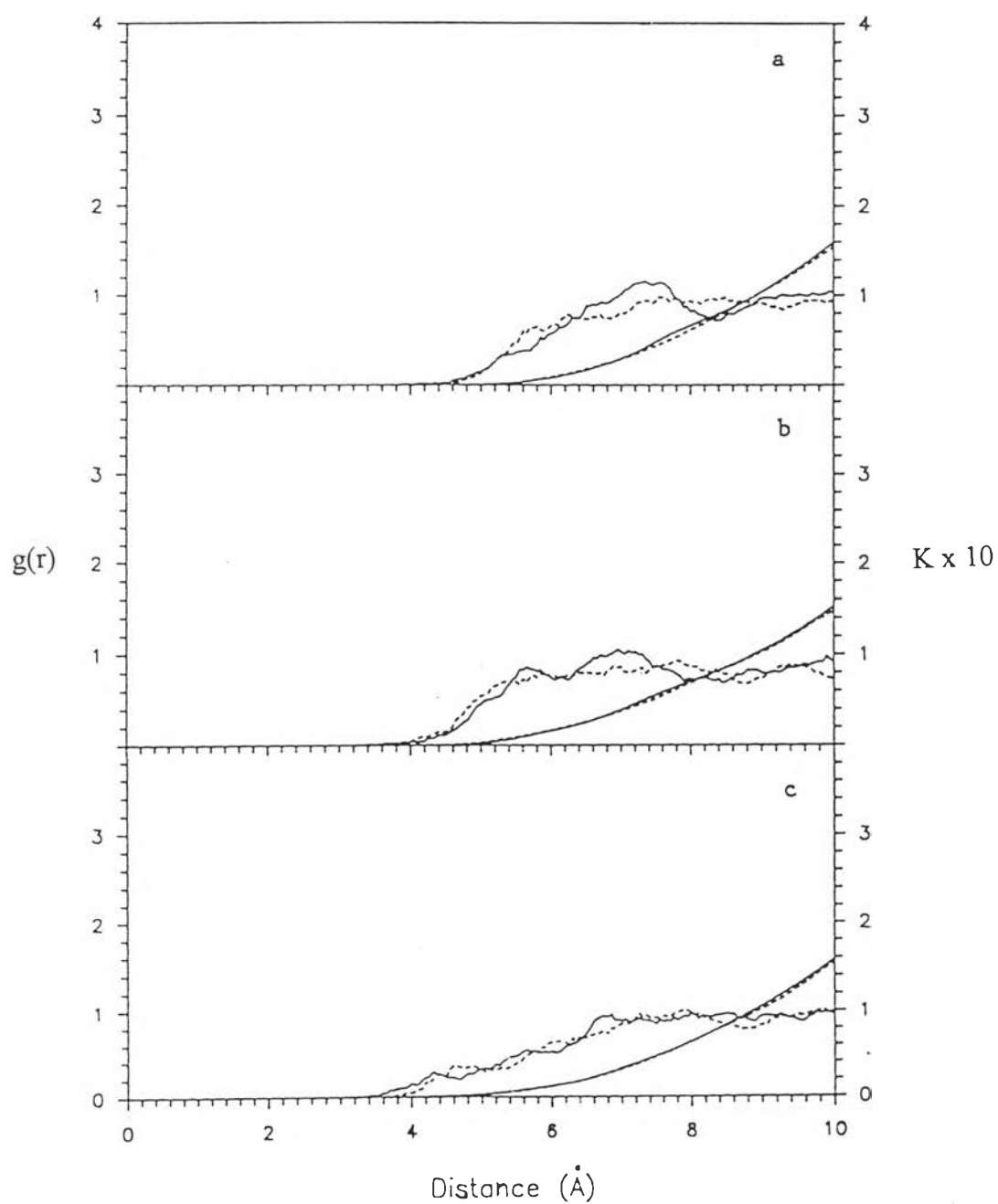
Figure 5.18 Calculated atom-O (—) and atom-H_O (---) radial distribution functions and running integration numbers of methanol molecules for (a) C, (b) H_C and (c) H'_C atoms of cyclen.
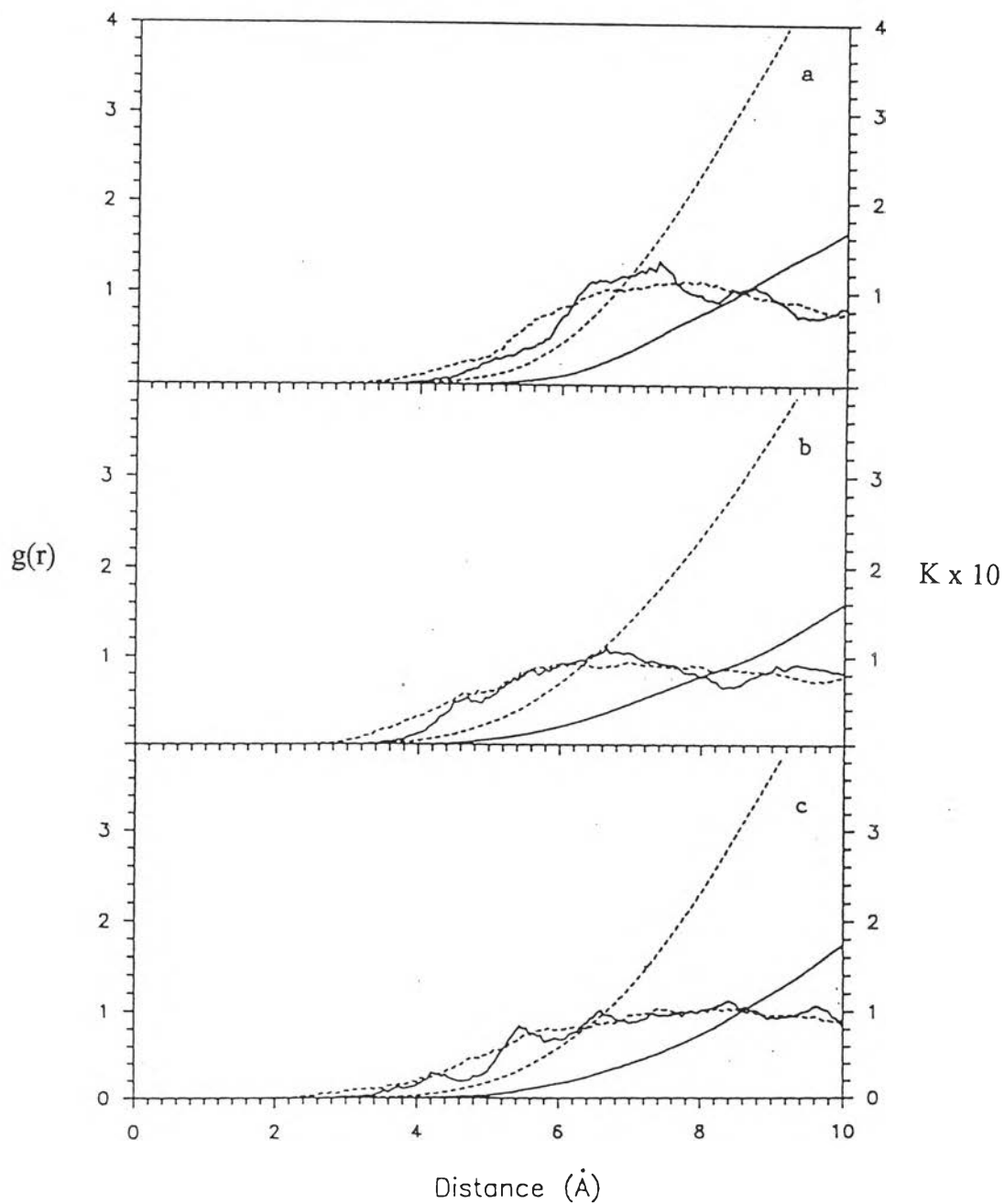
Figure 5.19 Calculated atom-C (—) and atom-H (---) radial distribution functions and running integration numbers of methanol molecules for (a) C, (b) H_C and (c) H'_C atoms of cyclen.